Use of *Tröger*'s Base as a Scaffold for New Chiral Molecular Tweezers: Synthesis of Trimeric, Fused *Tröger*'s Bases[1])

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

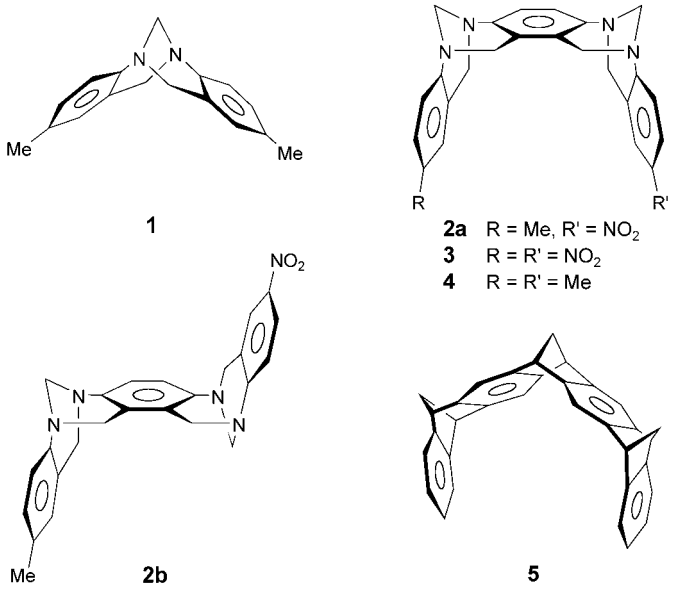
Four novel molecular tweezers, **6**–**9**, have been synthesized having, for the first time, three fused *Tröger*'s bases. The compounds differ in the relative configuration of the three fused methylene bridges and have been unambiguously characterized by NMR.

Introduction. – *Tröger*'s base (**1**) [1] is a concave chiral molecule, the chirality of which results from the blocked configuration of its stereogenic N-atoms. *Tröger*'s base and its derivatives have been described as '*fascinating molecules*' [2]. They provide relatively rigid chiral frameworks for the construction of chelating and biomimetic systems, which were essentially developed by *Wilcox* and co-workers, and elaborated by others [3]. *Tröger*'s bases show a perpendicular arrangement of the two aromatic rings [3c], as in *Kagan*'s ether, which was used by *Harmata* and co-workers for the synthesis of molecular tweezers [4]. In this context, we have utilized the *Tröger*'s base skeleton as a scaffold for the construction of the molecular clips **2** [5], **3** [6], and **4** [7].

In this paper, we report the synthesis of chiral molecular tweezers with a trimeric, fused *Tröger*'s base skeleton. During the course of the present work, *Klärner et al.* [8] have described the synthesis of another family of molecular tweezers of type **5**, with three methylene bridges, achiral carbocylic analogues of the compounds described in this paper.

Results and Discussion. – 1. *Synthesis.* The synthesis of the trimeric, fused tweezers **6**–**8** (*Scheme 1*) started from the dimer **2a**, with relative *syn* configuration of the CH_2 bridges, according to a synthetic pathway similar to the one used for the synthesis of **2a** [5]. Amine **10** was prepared from **2a** by two procedures; in the first one, **10** was obtained in 42% yield by hydrogenation over Pd/C, in the second one, it was prepared in almost quantitative yield by reducing **2a** with $SnCl_2$ in concentrated HCl. The reaction of **10** with '6-nitroisatoic anhydride'[2]) in anhydrous THF afforded amide **11** in 66% yield. The latter was reduced to amine **12** (40% yield) by treatment with the

[1]) Some preliminary results were described in T. Mas, C. Pardo, J. Elguero, *Mendeleev Commun.*, **2004**, 235.
[2]) Systematic name: 6-nitro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione.



borane-THF complex. Amine **12** was obtained in a higher yield, 71%, by reduction of **11** with the BH_3/Me_2S complex in THF. In the last step, the reaction of **12** with aqueous formaldehyde and concentrated HCl in EtOH at 90° for 40 h yielded a mixture from which were isolated the trimeric bases **6** (11%), **7** (7%), and **8** (8%).

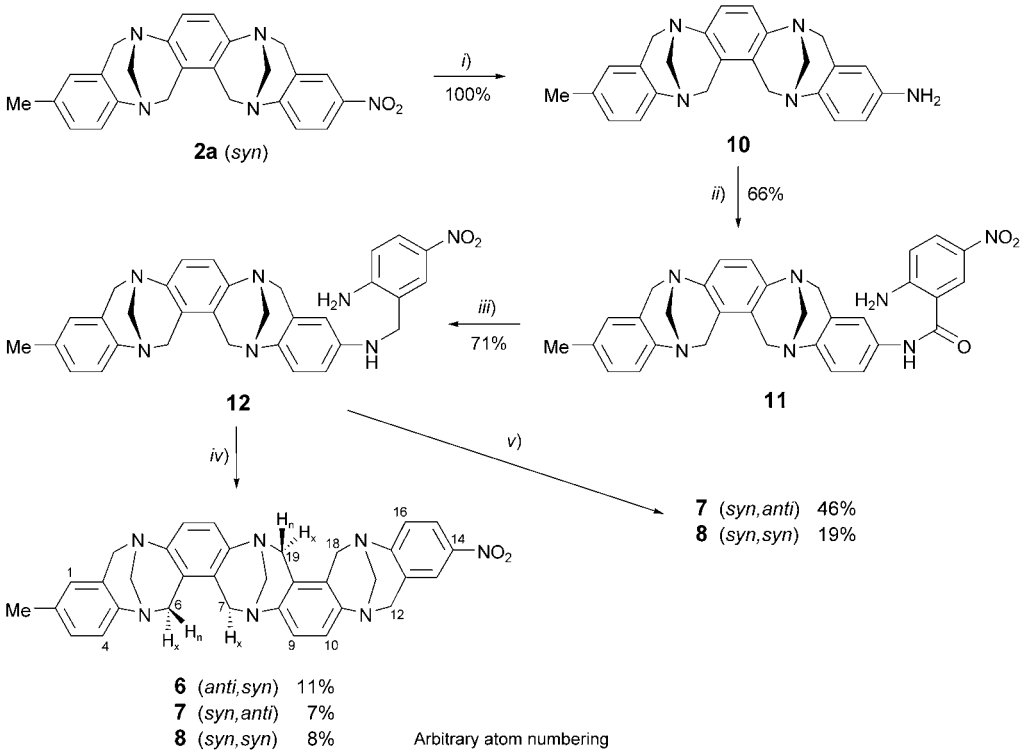
Alternatively, cyclization of **12** with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) at room temperature during 72 h afforded a mixture from which **7** (46%) and **8** (19%) were isolated. This reaction was cleaner than that with formaldehyde, and the purification of the reaction crude was easier (*Scheme 1*).

Starting from the *anti*-isomer **2b** (*Scheme 2*), we succeeded in obtaining the fourth stereoisomer, trimer **9**. Thus, hydrogenation of **2b** over Pd/C afforded the corresponding amino derivative **13** in 69% yield. The latter was transformed into amide **14** in 62% yield by reaction with 6-nitroisatoic anhydride in THF, and amide **14** was then reduced in 45% yield to amine **15** using BH_3/Me_2S in THF. Treatment of **15** with HMTA in TFA at room temperature for 48 h yielded a mixture from which **9** (33%) and **6** (19%) were isolated.

Compound **7** was quantitatively isomerized at 80° in HCl to a 1:2:2:2 mixture of **9**/**6**/**7**/**8** (according to ^{1}H-NMR analysis). This result is similar to those obtained in isomerization experiments of the dimeric bases **2** [5] and **4** [7].

2. *Structure Elucidation*. The structures of the new trimeric *Tröger*'s bases were established by HR-MS, and ^{1}H- and ^{13}C-NMR (NOE, COSY, HMQC, HMBC) experiments based on previous studies of related *Tröger*'s bases [9][10]. The cyclization of amines **12** and **15** is always regioselective, as in the precedent cases [5–7][11], and the orientation of the cyclization has been determined by ^{1}H-NMR. H–C(9) and H–C(10) form an *AB* system, with a ^3J value of 8.7 Hz, corresponding to an *ortho* arrangement of aromatic H-atoms in **6**–**8**, and as an A_2 system in **9**. However, a NOE-

Scheme 1



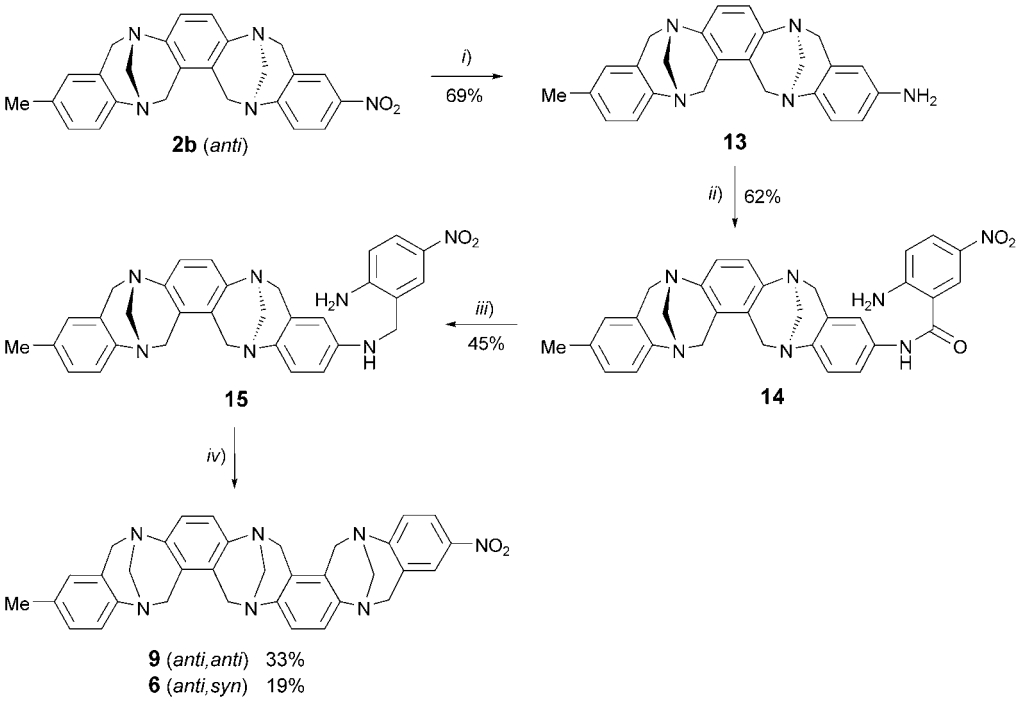
i) $SnCl_2$, HCl, EtOH, reflux, 1 h. *ii*) 6-Nitroisatoic anhydride[2]), THF, reflux, 4 h. *iii*) $BH_3 \cdot Me_2S$, THF, reflux, 8 h. *iv*) 37% aq. CH_2O, 95% EtOH, 36% aq. HCl, 90°, 40 h. *v*) Hexamethylenetetramine (HMTA), CF_3CO_2H (TFA), r.t., 72 h.

DIF experiment showed a correlation between $H_x-C(18)$ and $H_n-C(19)$ establishing that **9** is regiochemically identical to the other three isomers. The isomerization experiment also showed that the four bases must have the same connectivity.

We unequivocally assigned the relative configurations of **6**, **7**, **8**, and **9**, as *anti*,*syn*, *syn*,*anti*, *syn*,*syn* and *anti*,*anti*, repectively, based on the relative spatial disposition of contiguous methylene bridges, from their ^{1}H-NMR spectra (*Figure*). As shown in *Table 1*, long-range COSY experiments indicated a homoallylic ^5J coupling between the CH_2 H-atoms linked to the same *internal* aromatic ring, *i.e.*, $H-C(6)$ and $H-C(7)$ in **2a** and **2b**, whose structures were previously established [5]. In the *syn* arrangement of **2a**, a ^5J coupling is observed between the *exo* H-atom of one CH_2 H-atom and the *endo* H-atom of the other one. In the *anti*-isomer **2b**, homoallylic coupling is observed between both *exo* or *endo* protons. Likewise, we had observed a NOE interaction between $H_x-C(6)$ and $H_x-C(7)$ in the *syn* isomer **2a**, and between the *exo* H-atom of one CH_2 group, *e.g.,* $H_x-C(6)$, and the *endo* H-atom of the other one, *e.g.*, $H_n-C(7)$, in the *anti* arrangement of **2b**.

We have determined the homoallylic and, when possible, NOE correlations between the internal CH_2 resonances of the four diastereoisomeres **6**–**9** (*Table 1*) and,

Scheme 2



i) H_2, Pd/C, EtOH, r.t., 4 h. *ii*) 6-Nitroisatoic anhydride[2]), THF, reflux, 6 h. *iii*) $BH_3 \cdot Me_2S$, THF, reflux, 10 h. *iv*) HMTA, TFA, r.t., 48 h.

thus, could unequivocally assign the relative configurations. This assignment was also in agreement with the observation that, at room temperature, *syn*-**2a** gives rise to **7** and **8**, whereas *anti*-**2b** affords **6** and **9**, because isomerization of the starting dimeric base takes place only at high temperature [5–7].

Table 1. *Homoallylic Coupling and NOE Correlations Observed in Dimeric and Trimeric* Tröger*'s Bases.* At 500 MHz in (D_6)acetone.

Compound	^5J [Hz]	NOE	Rel. configuration
2a	6n,7x	6x/7x	*syn*
2b	6x,7x	6x/7n	*anti*
		7x/6n	
6	6x,7x		*anti*
	18x,19n	18x/19x	*syn*
7	6x,7n		*syn*
	18x,19x	19n/18x	*anti*
8	6x,7n		*syn*
	18x,19n	18x/19x	*syn*
9	6x,7x		*anti*
	18x,19x	18x/19n	*anti*

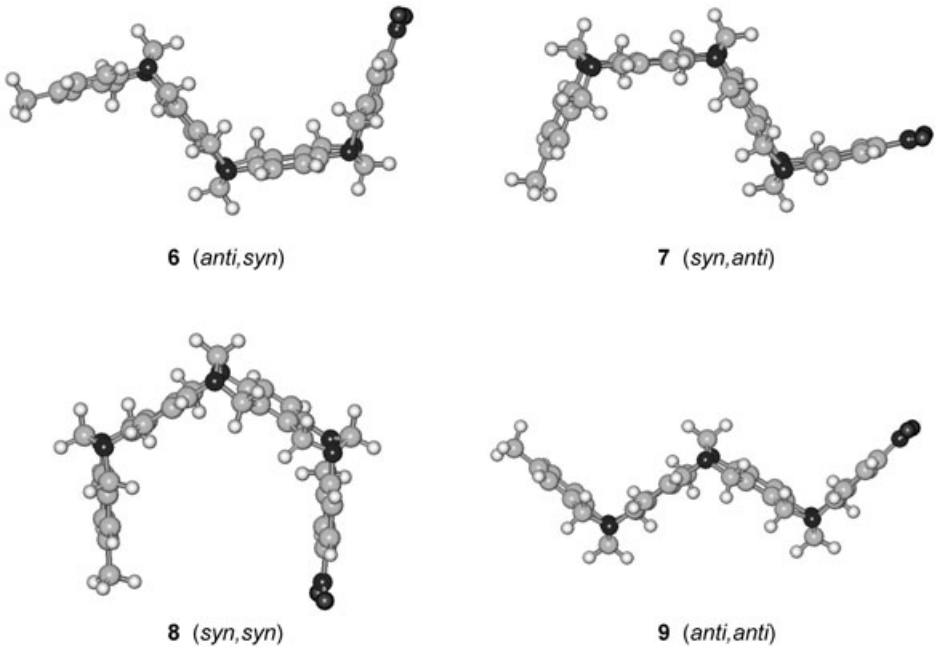


Figure. *Computer-generated structures of the four possible diastereoisomers* **6**–**9**

It has been reported [5] that, in dimeric *Tröger*'s bases, the aromatic H-atoms in the external rings are more shielded in *syn*-**2a** than in *anti*-**2b** in the corresponding ^{1}H-NMR spectra ($CDCl_3$). This characteristic could also be used to determine the configurations of **6**–**9**. As evident from *Table 2*, these H-atoms are shielded and deshielded most in **8** and **9**, respectively, and were, thus, assigned *syn*,*syn* and *anti*,*anti* configuration, respectively. For **6** and **7**, we observed that H–C(1) and H–C(3) in **6** are more deshielded than in **7**, but H–C(15) is more shielded, so we could assign *anti*,*syn*- and *syn*,*anti*-configurations, respectively. This criterion is less conclusive than the previous one, based on the homoallylic coupling and NOE correlations, because the chemical shifts are dependent on the solvent and on the concentration of the sample, which requires, for an unequivocal assignment, the presence of all stereoisomers, as in this work.

Table 2. *^{1}H-NMR Chemical Shifts* (in ppm) *of Aromatic, External-Ring H-Atoms.* At 500 MHz in (D_6)acetone.

Compound	H–C(1)	H–C(3)	H–C(4)	H–C(13)	H–C(15)	H–C(16)
2a	6.61	6.82	6.88	7.78[a])	7.89[b])	7.27[c])
2b	6.72	6.93	6.97	7.91[a])	8.00[b])	7.36[b])
6	6.68	6.90	6.92	7.83	7.92	7.30
7	6.65	6.86	6.93	7.83	7.95	7.30
8	6.45	6.71	6.79	7.69	7.81	7.15
9	6.72	6.92	6.98	7.90	7.99	7.35

[a]) H–C(12). [b]) H–C(10). [c]) H–C(9).

Conclusions. – We have reported the successful synthesis of the four new chiral molecular tweezers **6**–**9**. Compound **8**, with its cage structure, is the first example of a heterocyclic chiral molecular clip planed to be used in host–guest chemistry in the near future.

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Experimental Part

General. 6-Nitroisatoic anhydride[2]) was prepared from 5-nitroisatin according to a literature procedure [12], and was used without further purification. Melting points (m.p.) are uncorrected. IR Spectra: in cm^{-1}. ^{1}H-NMR Spectra were recorded at 200, 300, and 500 MHz, and ^{13}C-NMR spectra were recorded at 50, 75, and 125 MHz; chemical shifts δ in ppm rel. to internal Me_4Si, coupling constants J in Hz.

General Procedure (*GP 1*) *for the Hydrogenation of Compounds* **2**. The appropriate substrate **2** in EtOH was hydrogenated over 10% Pd/C at r.t. and at a pressure of 2 bar during the time indicated in each case. The mixture was filtered through *Celite*, which was washed with EtOH, and the resulting filtrate was evaporated to dryness under reduced pressure to afford the corresponding amino compounds after flash chromatography (FC) (SiO_2; AcOEt/MeOH 8:2).

syn-*23-Methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-amine* (**10**). Prepared according to *GP 1* from **2a** (300 mg, 0.71 mmol) in EtOH (45 ml) and Pd/C (150 mg) for 7 h. Yield: 42%. M.p. 203–205° (dec.). R_f (AcOEt/MeOH 8:2) 0.16. IR (KBr): 3420, 3348, 3200, 2941, 2891, 1622, 1497, 1475, 1342, 1213, 1069, 968, 949, 831. ^{1}H-NMR ($CDCl_3$): 2.21 (*s*, 3 H); 3.78 (*d*, *J* = 16.8, 1 H); 3.85 (*d*, *J* = 17.1, 1 H); 4.02 (*d*, *J* = 16.8, 1 H); 4.09 (*d*, *J* = 16.6, 1 H); 4.19–4.21 (*m*, 4 H); 4.34 (*d*, *J* = 16.8, 1 H); 4.38 (*d*, *J* = 17.1, 1 H); 4.58 (*d*, *J* = 16.8, 1 H); 4.63 (*d*, *J* = 16.6, 1 H); 6.18 (*d*, *J* = 2.6, 1 H); 6.47 (*dd*, *J* = 8.3, 2.6, 1 H); 6.70 (br. *s*, 1 H); 6.90 (*d*, *J* = 8.3, 1 H); 6.92–7.02 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 20.8; 55.77; 55.83; 57.8; 57.9; 66.4; 66.6; 112.3; 115.0; 124.1 (2 C); 124.8; 124.9; 125.0; 126.0; 127.1; 127.6; 128.2; 128.7; 133.6; 139.6; 142.8; 143.7; 143.8; 145.7. Anal. calc. for $C_{25}H_{25}N_5$: C 75.92, H 6.37, N 17.71; found: C 75.83, H 6.27, N 17.69.

anti-*23-Methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-amine* (**13**). Prepared according to *GP 1* from **2b** (100 mg, 0.24 mmol) in EtOH (25 ml) and Pd/C (75 mg) for 4 h. Yield: 69%. M.p. 260–265° (dec.). R_f (AcOEt/MeOH 8:2) 0.26. IR (KBr): 3339, 3215, 2947, 2899, 1618, 1497, 1474, 1329, 1217, 1074, 974, 961, 841. ^{1}H-NMR ($CDCl_3$): 2.24 (*s*, 3 H); 3.78 (*d*, *J* = 17.1, 1 H); 3.86 (*d*, *J* = 16.9, 1 H); 4.04 (*d*, *J* = 16.8, 1 H); 4.07–4.23 (*m*, 5 H); 4.27 (*d*, *J* = 17.1, 1 H); 4.32 (*d*, *J* = 16.9, 1 H); 4.56 (*d*, *J* = 16.8, 1 H); 4.62 (*d*, *J* = 16.6, 1 H); 6.22 (*d*, *J* = 2.5, 1 H); 6.53 (*dd*, *J* = 8.3, 2.5, 1 H); 6.74 (br. *s*, 1 H); 6.94 (*d*, *J* = 8.3, 1 H); 6.97–7.08 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$): 20.9; 55.6; 55.8; 58.0; 58.1; 66.2; 66.4; 112.3; 115.1; 124.2; 124.4; 124.5; 124.8; 124.9; 125.7; 127.2; 127.3; 128.3; 134.1; 143.7; 144.9. Anal. calc. for $C_{25}H_{25}N_5$: C 75.92, H 6.37, N 17.71; found: C 76.10, H 6.18, N 17.53.

Reduction of **2a** *with Stannous Chloride*. To a mixture of **2a** (80 mg, 0.19 mmol) and $SnCl_2 \cdot 2\,H_2O$ (186 mg, 0.83 mmol) were added, at r.t. under Ar gas, anh. EtOH (1.5 ml) and then 36% aq. HCl (1.5 ml). The mixture was refluxed for 1 h and cooled to r.t. Then, 12M aq. NaOH soln. (15 ml) was added, the mixture was refluxed for 1 h, kept overnight at r.t., and extracted with CH_2Cl_2 (3 × 15 ml). The org. layer was washed with H_2O (20 ml), dried ($MgSO_4$), and evaporated under reduce pressure to yield almost pure **10** quantitatively.

General Procedure (*GP 2*) *for the Synthesis of Amides* **11** *and* **14**. 6-Nitroisatoic anhydride[2]) was added in small portions at r.t. and Ar atmosphere to a soln. of the free amine (**10** or **13**) in anh. THF. The mixture was heated at reflux for the time indicated, and evaporated to dryness under reduced pressure. FC (SiO_2) of the crude afforded the pure amides.

2-Amino-N-*(*syn-*23-methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-yl)-5-nitrobenzamide* (**11**). Prepared according to *GP 2* from **10** (1.15 g, 2.91 mmol) in THF (8 ml) and 6-nitroisatoic anhydride[2]) (605 mg, 2.91 mmol) for 4 h, followed by FC (SiO_2; AcOEt/MeOH 98:2). Yield: 66%. M.p. > 350° (dec.). IR (KBr): 3450, 3331, 2941, 2893, 1655, 1618, 1589, 1497, 1474, 1323, 1213, 1126, 1105, 833. ^{1}H-NMR ((D_6)DMSO): 2.08 (*s*, 3 H); 3.85 (2*d*, 2 H); 3.96 (*d*, 1 H); 4.00 (*d*, 1 H); 4.08–4.13 (*m*, 4 H); 4.30 (2*d*, 2 H); 4.50 (*d*, *J* = 16.4, 1 H); 4.56 (*d*, *J* = 16.8, 1 H); 6.63 (br. *s*, 1 H); 6.80 (*d*, *J* = 9.3, 1 H); 6.87–6.98 (*m*, 3 H); 7.04 (*d*, *J* = 8.6, 1 H); 7.27 (*d*, *J* = 2.2, 1 H); 7.36 (*dd*, *J* = 8.6, 2.2, 1 H); 7.53 (br. *s*, 2 H); 8.03 (*dd*, *J* = 9.3, 2.4, 1 H); 8.46 (*d*, *J* = 2.4, 1 H); 10.20 (*s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 19.8; 55.09; 55.11; 57.0; 57.2;

65.37; 65.43; 113.5; 115.1; 118.3; 119.4; 122.9; 123.0; 123.9; 124.1; 124.2; 124.3; 125.59; 126.63; 126.9; 127.0; 127.1; 127.4; 131.9; 133.7; 134.4; 142.6; 142.8; 143.8; 145.2; 154.4; 165.0. Anal. calc. for $C_{41}H_{37}N_9O_3$: C 69.97, H 5.30, N 17.91; found: C 70.03, H 5.21, N 17.88.

2-Amino-N-(anti-*23-methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-yl)-5-nitrobenzamide* (**14**). Prepared according to *GP 2* from **13** (70 mg, 0.18 mmol) in THF (1.5 ml) and 6-nitroisatoic anhydride[2]) (55 mg, 0.26 mmol) for 6 h, followed by FC (SiO_2; AcOEt/MeOH 9:1). Yield: 62%. M.p. 360–364° (dec.). IR (KBr): 3449, 3339, 2930, 2897, 1655, 1618, 1591, 1497, 1475, 1325, 1219, 1190, 1128, 837. ^{1}H-NMR ((D$_6$)DMSO): 2.15 (*s*, 3 H); 3.78 (*d*, *J* = 16.7, 1 H); 3.81 (*d*, *J* = 16.8, 1 H); 3.95–4.14 (*m*, 6 H); 4.31 (2*d*, 2 H); 4.49 (*d*, *J* = 16.3, 1 H); 4.55 (*d*, *J* = 16.3, 1 H); 6.72 (br. *s*, 1 H); 6.82 (*d*, *J* = 9.3, 1 H); 6.89–6.98 (*m*, 4 H); 7.07 (*d*, *J* = 8.7, 1 H); 7.30 (*d*, *J* = 2.2, 1 H); 7.39 (*dd*, *J* = 8.7, 2.2, 1 H); 7.62 (br. *s*, 2 H); 8.05 (*dd*, *J* = 9.3, 2.6, 1 H); 8.54 (*d*, *J* = 2.6, 1 H); 10.29 (*s*, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 19.9; 54.85; 54.86; 57.3; 57.5; 65.1; 65.2; 113.0; 115.4; 118.6; 119.8; 123.07; 123.14; 124.2; 124.4; 124.5; 124.7; 125.7; 126.5; 127.1; 127.2; 127.3; 127.6; 131.8; 133.6; 134.4; 142.8; 143.0; 144.0; 145.3; 154.7; 165.3. Anal. calc. for $C_{41}H_{37}N_9O_3$: C 69.97, H 5.30, N 17.91; found: C 70.19, H 5.33, N 17.69.

General Procedure (*GP 3*) *for the Reduction of the Amides* **11** *and* **14**. A 10M $BH_3 \cdot Me_2S$ soln. (220 µl, 2.2 mmol) was added dropwise at 0° under Ar gas to a suspension of the corresponding amide (0.37 mmol) in anh. THF (3 ml). The mixture was heated at reflux for the time indicated. Then. 6M aq. HCl soln. (14 ml) was added dropwise at 0°, and the mixture was stirred at r.t. for 2–3 h. The soln. was made basic at 0° with 6M aq. NH_3 soln. (pH 11), and extracted with CH_2Cl_2 (3 × 15 ml). The org. layer was washed with H_2O (15 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to FC (SiO_2) to afford the pure amine (**12** or **15**).

syn-N-*(2-Amino-5-nitrobenzyl)-23-methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-amine* (**12**). Prepared according to *GP 3*, for 3 h, followed by FC (SiO_2; AcOEt/MeOH 9:1). Yield: 71%. M.p. 225–228° (dec.). IR (KBr): 3420, 3352, 2939, 2891, 1618, 1585, 1497, 1474, 1439, 1313, 1213, 1101, 833. ^{1}H-NMR ($CDCl_3$): 2.23 (*s*, 3 H); 3.79 (*d*, *J* = 16.9, 1 H); 3.85 (*d*, *J* = 17.1, 1 H); 4.06 (*d*, *J* = 17.1, 1 H); 4.09 (*d*, *J* = 16.6, 1 H); 4.11–4.21 (*m*, 4 H); 4.36 (*d*, *J* = 16.9, 1 H); 4.39 (*d*, *J* = 17.1, 1 H); 4.62 (*d*, *J* = 16.6, 1 H); 4.64 (*d*, *J* = 17.1, 1 H); 4.98 (br. *s*, 2 H); 6.26 (*d*, *J* = 2.6, 1 H); 6.54 (*dd*, *J* = 8.5, 2.6, 1 H); 6.61 (*d*, *J* = 9.5, 1 H); 6.72 (br. *s*, 1 H); 6.92–7.03 (*m*, 5 H); 8.01–8.07 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 20.8; 47.7; 55.77; 55.82; 57.8; 58.0; 66.3; 66.5; 111.2; 114.31; 114.34; 121.4; 124.1 (2 C); 124.77; 124.82; 125.1; 125.6; 126.2; 126.3; 127.1; 127.7; 128.1; 129.0; 133.6; 138.6; 140.4; 143.73; 143.76; 144.2; 145.8; 152.3. Anal. calc. for $C_{41}H_{39}N_9O_2$: C 71.39, H 5.70, N 18.27; found: C 71.20, H 5.81, N 18.11.

anti-N-*(2-Amino-5-nitrobenzyl)-23-methyl-1,6,14,19-tetraazaheptacyclo[17.7.1.1^{6,14}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,25}]octacosa-2,4,8,10,12,16,20,22,24-nonaen-10-amine* (**15**). Prepared according to *GP 3*, for 2 h, followed by FC (SiO_2; AcOEt). Yield: 45%. M.p. 240–243° (dec.). IR (KBr): 3440, 3377, 2930, 2897, 1618, 1585, 1497, 1474, 1437, 1327, 1217, 1190, 1099, 841. ^{1}H-NMR ($CDCl_3$): 2.25 (*s*, 3 H); 3.80 (*d*, *J* = 16.6, 1 H); 3.86 (*d*, *J* = 16.7, 1 H); 4.06–4.20 (*m*, 6 H); 4.30 (*d*, *J* = 16.6, 1 H); 4.33 (*d*, *J* = 16.7, 1 H); 4.62 (*d*, *J* = 16.9, 1 H); 4.63 (*d*, *J* = 16.9, 1 H); 4.99 (br. *s*, 2 H); 6.30 (*d*, *J* = 2.5, 1 H); 6.58–6.66 (*m*, 2 H) 6.74 (br. *s*, 1 H); 6.98–7.07 (*m*, 5 H); 8.03–8.08 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 20.9; 47.6; 55.87; 55.91; 58.3; 58.5; 66.4; 66.5; 111.3; 114.3; 114.4; 121.5; 124.27; 124.29; 124.9; 125.02; 125.05; 125.6; 126.1; 126.3; 127.3; 127.6; 128.2; 129.0; 133.8; 138.8; 140.4; 143.76; 143.83; 144.2; 145.6; 152.2. Anal. calc. for $C_{41}H_{39}N_9O_2$: C 71.39, H 5.70, N 18.27; found: C 71.47, H 5.92, N 18.33.

Synthesis of the Trimeric Diastereoisomers **6**–**8** *with Formaldehyde.* At r.t. under Ar gas, to a stirred suspension of **12** (180 mg, 0.33 mmol) in 95% EtOH (1 ml) were successively added 35–40% aq. formaldehyde soln. (147 µl) and 36% aq. HCl soln. (169 µl). The mixture was heated at reflux for 40 h, cooled to r.t., and made basic with conc. aq. NH_3 soln. (pH 11). The alkaline soln. was extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. extracts were washed with H_2O (15 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The crude was purified by FC (SiO_2; AcOEt/MeOH 98:2) to yield, in this order, **6** (11%), **7** (7%), and **8** (8%).

Data of anti,syn-*10-Methyl-28-nitro-1,6,14,19,24,32-hexaazadecacyclo[17.17.1.1^{6,14}.1^{24,32}.0^{2,17}.0^{5,16}.0^{8,13}.0^{20,35}.0^{23,34}.0^{26,31}]nonatriaconta-2,4,8,10,12,16,20,22,26,28,30,34-dodecaene* (**6**). M.p. 280–285° (dec.). R_f (SiO_2; AcOEt/MeOH 8:2) 0.40. IR (KBr): 1612, 1578, 1516, 1495, 1472, 1340, 1219, 1204, 1074, 961, 939, 841. ^{1}H-NMR ((D$_6$)acetone): 2.15 (*s*, 3 H); 3.80 (*d*, *J* = 16.6, 1 H); 3.82 (*d*, *J* = 16.8, 1 H); 3.92 (*d*, *J* = 11.4, 1 H); 3.99 (*d*, *J* = 17.1, 2 H); 4.01 (*s*, 2 H); 4.02 (*d*, *J* = 11.4, 1 H); 4.20 (*d*, *J* = 16.9, 1 H); 4.21 (*d*, *J* = 16.9, 1 H); 4.24 (*s*, 2 H); 4.27 (*d*, *J* = 17.1, 1 H); 4.28 (*d*, *J* = 17.0, 1 H); 4.31 (*d*, *J* = 16.6, 1 H); 4.47 (*d*, J = 17.1, 1 H); 4.51 (*d*, *J* = 17.2, 1 H); 4.72 (*d*, *J* = 17.0, 1 H); 6. 68 (br. *s*, 1 H); 6.81 (*s*, 2 H); 6.90 (*dd*, *J* = 8.2, 1 H); 6.92 (*d*, *J* = 8.2, 1 H); 6.98 (*d*, *J* = 8.7, 1 H); 6.99 (*d*, *J* = 8.7, 1 H); 7.30 (*d*, *J* = 8.9, 1 H); 7.83 (*d*, *J* = 2.4, 1 H); 7.92 (*dd*, *J* = 8.9, 2.5, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.8; 55.8; 56.1; 56.4; 56.8; 58.5; 59.0; 66.5; 66.76; 66.83; 122.9; 123.6; 124.68; 124.70; 125.0;

125.3; 125.5; 125.7; 126.06; 126.10; 126.2; 126.8; 127.8; 128.5; 128.8; 130.6; 133.6; 143.8; 144.2; 144.82; 144.86; 145.4; 147.1; 156.5. HR-FAB-MS: 569.2549 ($C_{34}H_{31}N_7O_2$): 570.2616 ($[M+1]^+$, $C_{34}H_{32}N_7O_2^+$; calc. 570.2618).

Data of **7**. M.p. 265–267° (dec.). R_f (AcOEt/MeOH 8:2) 0.35. IR (KBr): 1611, 1582, 1516, 1495, 1472, 1340, 1221, 1202, 1072, 962, 939, 841. ^{1}H-NMR ((D$_6$)acetone): 2.09 (*s*, 3 H); 3.81 (*d*, *J* = 16.8, 1 H); 3.94 (*d*, *J* = 17.7, 1 H); 3.96 (*d*, *J* = 17.1, 1 H); 3.97 (*d*, *J* = 12.4, 1 H); 4.02 (*d*, *J* = 16.4, 1 H); 4.03 (*d*, *J* = 11.7, 1 H); 4.05 (*d*, *J* = 16.4, 1 H); 4.09 (*s*, 2 H); 4.12 (*d*, *J* = 12.4, 1 H); 4.16 (*d*, *J* = 12.4, 1 H); 4.21 (*d*, *J* = 17.0, 1 H); 4.30 (*d*, *J* = 17.2, 2 H); 4.34 (*d*, *J* = 17.1, 2 H); 4.55 (*d*, *J* = 16.7, 1 H); 4.63 (*d*, *J* = 17.0, 1 H); 6.65 (br. *s*, 1 H); 6.85 (*d*, *J* = 8.6, 1 H); 6.86 (pseudo-*d*, *J* = 6.7, 1 H); 6.88 (*d* , *J* = 8.7, 1 H); 6.93 (pseudo-*d*, *J* = 9.8, 2 H); 6.96 (*d*, *J* = 8.7, 1 H); 7.30 (*d*, *J* = 8.9, 1 H); 7.83 (*d*, *J* = 2.5, 1 H); 7.95 (*dd*, *J* = 8.9, 2.6, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.7; 55.9; 56.2; 56.5; 56.7; 58.7; 58.9; 66.2; 66.5; 67.3; 122.9; 123.6; 124.6; 124.8; 124.9; 125.4; 125.6; 125.8; 125.97; 126.01; 126.3; 126.6; 127.8; 128.6; 128.9; 130.5; 133.7; 143.9; 144.2; 144.8; 144.9; 145.4; 147.2; 156.6. HR-FAB-MS: 569.2531 ($C_{34}H_{31}N_7O_2$): 570.2594 ($[M+1]^+$, $C_{34}H_{32}N_7O_2^+$; calc. 570.2618).

Data of **8**. M.p. 250–252°. R_f (SiO_2; AcOEt/MeOH 8:2) 0.20. IR (KBr): 1612, 1582, 1512, 1497, 1472, 1339, 1219, 1070, 970, 947, 835. ^{1}H-NMR ((D$_6$)acetone): 1.98 (*s*, 3 H); 3.88 (*d*, *J* = 16.9, 1 H); 3.89 (*d*, *J* = 16.7, 1 H); 3.95 (*d*, *J* 17.1, 1 H); 4.01 (pseudo-*d*, *J* = 16.0, 1 H); 4.03 (*s*, 2 H); 4.04 (pseudo-*d*, *J* = 14.01, 1 H); 4.08 (*d*, *J* = 11.2, 1 H); 4.11 (*d*, *J* = 16.9, 1 H); 4.14 (pseudo-*d*, *J* = 14.7, 1 H); 4.16 (*s*, 2 H); 4.29 (*d*, *J* = 17.1, 1 H); 4.31 (*d*, *J* = 16.9, 1 H); 4.32 (*d*, *J* = 17.2, 1 H); 4.46 (pseudo-*d*, *J* = 15.8, 2 H); 4.63 (*d*, *J* = 16.9, 1 H); 6.45 (br. *s*, 1 H); 6.71 (br. *d*, *J* = 8.1, 1 H); 6.79 (*d*, *J* = 8.1, 1 H); 6.85 (*s*, 2 H); 6.89 (*d*, *J* = 8.6, 1 H); 6.91(*d*, *J* = 8.8, 1 H); 7.15 (*d*, *J* = 8.8, 1 H); 7.69 (*d*, *J* = 2.2, 1 H); 7.81 (*dd*, *J* = 8.8, 2.4, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.6; 55.7; 55.8; 56.4; 56.5; 58.2; 58.6; 66.6; 66.7; 67.2; 122.7; 123.6; 124.4; 124.6; 125.0; 125.3; 125.4; 125.7; 125.77; 125.79; 126.1; 126.6; 127.8; 128.38; 128.39; 130.0; 133.8; 143.8; 144.2; 144.72; 144.74; 145.4; 146.8; 156.1. HR-FAB-MS: 569.2540 ($C_{34}H_{31}N_7O_2$): 570.2610 ($[M+1]^+$, $C_{34}H_{32}N_7O_2^+$; calc. 570.2618).

Synthesis of the Trimeric Diastereoisomers **6**, **8**, *and* **9** *with HMTA in TFA*. Hexamethylenetetramine (HMTA; 1.92 mmol) was added at 0° under Ar gas to a suspension of the corresponding amine (**12** or **15**; 1.75 mmol) in anh. trifluoroacetic acid (TFA; 15 ml). The mixture was stirred at r.t. during the time indicated, and poured on cold H_2O (25 ml). The soln. was carefully made alkaline at 0° with 25% aq. NH_3 soln. (pH 11), and extracted with CH_2Cl_2 (3 × 50 ml). The org. layer was washed with H_2O (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The crude was purified by FC (SiO_2). From **12**, after 72 h, followed by FC (AcOEt/MeOH 93:7), isomers **7** (46%) and **8** (19%) were isolated. From **15**, after 48 h, followed by FC (CH_2Cl_2/MeOH 98.5:1.5), **9** (33%) and **6** (19%) were isolated in this order, resp.

Data of **9**. M.p. 315–318° (dec.). R_f (AcOEt/MeOH 8:2) 0.35. IR (KBr): 1611, 1580, 1516, 1495, 1472, 1339, 1221, 1202, 1074, 961, 939, 845. ^{1}H-NMR ((D$_6$)acetone): 2.17 (*s*, 3 H); 3.88 (pseudo-*d*, *J* = 16.6, 3 H); 3.97 (*d*, *J* = 12.4, 1 H); 4.01 (*d*, *J* = 12.7, 1 H); 4.07 (*d*, *J* = 16.7, 1 H); 4.11 (pseudo-*d*, *J* = 15.2, 2 H); 4.16 (*d J* = 12.4, 1 H); 4.22 (*s*, 2 H); 4.28 (pseudo-*d*, *J* = 19.1, 1 H); 4.30 (pseudo-*d*, *J* = 18.6, 1 H); 4.32 (*d*, *J* = 17.0, 1 H); 4.34 (*d*, *J* = 17.5, 1 H); 4.51 (*d*, *J* = 16.9, 1 H); 4.55 (*d*, *J* = 16.6, 1 H); 4.71 (*d*, *J* = 16.9, 1 H); 6.72 (br. *s*, 1 H); 6.92 (*d*, *J* = 8.6, 1 H); 6.93 (pseudo-*d*, *J* = 5.6, 1 H); 6.95 (*d*, *J* = 9.5, 1 H); 6.96 (*s*, 2 H); 6.98 (*d*, *J* = 8.1, 1 H); 7.35 (*d*, *J* = 8.9, 1 H); 7.90 (*d*, *J* = 2.5, 1 H); 7.99 (*dd*, *J* = 8.9, 2.5, 1 H). ^{13}C-NMR ((D$_6$)acetone): 20.8; 56.1; 56.2; 56.5; 56.7; 58.7; 59.0; 66.4; 66.6; 67.11; 123.0; 123.6; 124.82; 124.85; 124.9; 125.4; 125.68; 125.74; 126.1; 126.2; 126.4; 126.6; 127.9; 128.4; 128.6; 130.6; 133.7; 143.9; 144.2; 144.8; 144.9; 145.3; 147.1; 156.6. HR-FAB-MS: 569.2551 ($C_{34}H_{31}N_7O_2$): 570.2623 ($[M+1]^+$, $C_{34}H_{32}N_7O_2^+$; calc. 570.2618).

Isomerization of **7**. A soln. of **7** (20 mg, 0.035 mmol) in 95% EtOH (2 ml) containing 36% aq. HCl soln. (150 µl, 1.8 mmol) was stirred at 80° for 36 h. The mixture was cooled to r.t., poured on H_2O, made basic with 25% aq. NH_3 soln. (pH 11), and extracted with CH_2Cl_2. The org. layer was washed with H_2O, dried ($MgSO_4$), and evaporated under reduced pressure to afford, in quantitative yield, a **9**/**6**/**7**/**8** 1:2:2:2 mixture of diastereoisomers (determined by ^{1}H-NMR).

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